REMARKS

Applicants have amended the specification to include section headings and a detailed description of the drawings. The latter amendment is supported by the specification at page 6, lines 1-2. Applicants acknowledge withdrawal of the restriction requirement. Claims 1-7 are currently pending.

The examiner rejects claims 1-4 under 35 USC §112, ¶2/§101 as reciting a use without setting forth any steps involved in the method or process of that use. These claims are amended above to claim a method for treating certain septic disorders by the administration of a TNF antagonist. The amendment is supported in the specification at page 3, lines 1-2 and page 5, lines 36-37. Applicants additionally substitute the term "kit" for "commercial pack" in claims 4-5, and request that the rejection of claims 1-4 under §112¶2/§101 and 4-5 under §112¶2 be withdrawn.

The examiner rejects claims 1-4 and 7 under 35 USC §102(e) as anticipated by Stenzel et al. (US 6,235,281). This rejection is respectfully traversed. Applicants submit that Stenzel does not teach the administration of a TNF antagonist after a period of IL-6 *increase*, and therefore does not teach all elements of the present invention as claimed. Since "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," Stenzel cannot anticipate the presently claimed invention. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The examiner characterizes the present invention as "directed to the use of TNF

antagonists for the production of drugs for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6)" (paper 6:¶7a). While these particular elements are, in fact, part of the presently claimed invention, claim 1 (both as amended and as originally filed) includes the further limitation that "the serum level of interleukin-6 *increases* in a measurement period of at least thirty minutes" (claim 1, emphasis added). The examiner's recitation of Stenzel does not indicate that such selective administration is advised or contemplated (paper 6:¶7a).

Rather, suggestion is made that "[i]t is also routine in the management of patients with chronic conditions, to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels" (*id*). This statement does *not*, however, link monitoring proinflammatory cytokines to Stenzel, nor does it indicate that Stenzel teaches administering TNF antagonists solely when the IL-6 level is increasing. This reference is, in fact, silent on whether administration is more effective after an IL-6 increase, decrease or where the level remains constant. Further, no indication of a proper period of time for measuring the IL-6 level is given.

Stenzel teaches that administration of TNF antagonists is particularly effective where IL-6 levels are elevated. It does not teach, or even suggest, that treatment after a period of IL-6 *increase* would be more or less effective than at any other point in time. Accordingly, not only does Stenzel not anticipate claims 1-4 and 7 under 35 USC §102(e), but these claims would not be obvious over that reference under 35 USC §103(a). Applicants respectfully request that the rejection of claims 1-4 and 7 under 35 USC §102(e), as anticipated by Stenzel, be withdrawn.

The examiner rejects claims 5-6 under 35 USC §103(a) as unpatentable over Stenzel et al. (US 6,235,281). This rejection is respectfully traversed. Applicants reiterate that Stenzel does not teach administration of a TNF antagonist after a period of IL-6 increase, and further submit no suggestion or motivation to add this limitation exists either in Stenzel or in the art as a whole. Some suggestion or motivation to modify the reference is required, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As neither Stenzel nor any other prior art suggests this element of the base claim from which claims 5-6 depend, they cannot be obvious over this disclosure.

Stenzel teaches treatment of septicemia with a TNF antagonist in patients having elevated IL-6 serum levels. No statement is given therein to suggest that any indication other than a static reading of this serum level is necessary to optimally practice that invention. As indicated in the present specification, though, that and other research shows that certain cases of sepsis could be successfully treated with TNF antagonists, while others couldn't (specification p.2:31-34). Uncertainty still existed also as to the role IL-6 had in sepsis, with scientists taking contrary positions. Applicants submit that this demonstrates the need then extant in the art for a diagnostic method to determine those patients that would most benefit from TNF antagonist treatment.

The present invention fills this need in a manner not suggested by the prior art. It was surprisingly found that the mortality of patients having an increasing IL-6 serum level was lower than that where the IL-6 level was decreasing. Accordingly, where the

prior art was uncertain, the present invention demonstrates increased certainty as to treatment of sepsis patients with TNF antagonists. The specification states that

> It is evident that there are cases of sepsis which can be treated successfully with TNF antagonists, while in other cases treatment with TNF antagonists is not successful and is in fact contraindicated.
>
> It is an object of the present invention to identify, reliably and rapidly, those patients suffering from sepsis who can be successfully treated with TNF antagonists.

(2:30-38.) The fact that this increased certainty is tied to the increasing concentration of IL-6 serum levels is not suggested anywhere in Stenzel or in the knowledge generally held by those of skill in the art. Applicants respectfully request that the rejection of claims 5 and 6 under 35 USC §103(a) be withdrawn.

The examiner further rejects claims 1-7 under the common-law doctrine of obviousness-type double patenting over claims 1-3 of Stenzel et al. (US 6,235,281). This rejection is respectfully traversed. As stated above, neither the claims nor the specification of Stenzel teaches tying treatment with TNF antagonists to an increase in IL-6 serum levels. Also as demonstrated above, and in the specification, no suggestion of this additional criterion for treatment was found in the knowledge generally held. Rather, the implications of relative IL-6 serum levels was in dispute, and the merits of treatment coinciding with an increase or a decrease therein was uncertain. Accordingly, the claim element requiring

> ... the serum level of interleukin-6 [to increase] in a measurement period of at least thirty minutes ...

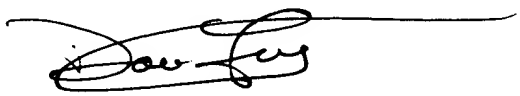
(claim 1) is not an obvious variation of Stenzel's claims 1-3. Applicants respectfully

request that the rejection of claims 1-7 under the common law doctrine of obviousness-type double patenting be withdrawn.

In view of the foregoing amendments and remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
KEIL & WEINKAUF



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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE SPECIFICATION

Please amend line 1 of page 1 to read as follows:

TITLE OF THE INVENTION

The use of TNF antagonists as drugs for treating septic disorders.

Please amend the paragraph found on lines 5-6 of page 1 to read as follows:

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The present invention relates to the use of TNF antagonists for treating septic disorders.

Please amend the paragraph found on lines 8-10 of page 1 to read as follows:

2. DESCRIPTION OF THE RELATED ART

It is known that the term tumor necrosis factor (TNF) embraces two cytotoxic factors (TNF-α and TNF-β) which are mostly produced by activated lymphocytes and monocytes.

Please amend the paragraph found on lines 36-38 of page 2 to read as follows:

BRIEF SUMMARY OF THE INVENTION

It is an object of the present invention to identify, reliably and rapidly, those patients suffering from sepsis who can be successfully treated with TNF antagonists.

Please amend the paragraph found on lines 4-7 of page 3 to read as follows:

BRIEF DESCRIPTION OF THE DRAWINGS

The figure shows that a decrease in mortality can be achieved by the treatment in the group with increasing IL-6 level.

DETAILED DESCRIPTION OF THE INVENTION

The treatment is preferably carried out on patients whose serum level of interleukin-6 in the measurement period is at least 500 pg/ml. However, it may also be distinctly higher than this level and be up to the order of a few mg/ml.

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS

Please amend claims 1-6 to read as follows:

1.(amended) A method [The use of TNF antagonists for producing drugs] for treating those septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes, which comprises administering a therapeutically effective amount of a tumor necrosis factor (TNF) antagonist.

2.(amended) The method [use] as claimed in claim 1, wherein the serum level of interleukin-6 is 500 pg/ml and above in the measurement period.

3.(amended) The method [use] as claimed in claim 1, wherein the measurement period is 4-10 hours.

4.(amended) The method [use] as claimed in claim 1, wherein an $F(ab')_2$ fragment of a monoclonal anti-TNF antibody is used as TNF antagonist.

5.(amended) A kit [commercial pack] comprising a TNF antagonist together with instructions for the use of this TNF antagonist for treating septic disorders where the serum level of IL-6 increases in a measurement period of at least thirty minutes.

6.(amended) A kit [commercial pack] as claimed in claim 5, wherein a monoclonal anti-TNF antibody is used as TNF antagonist.

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE ABSTRACT

Please amend the abstract as follows:

[The use of TNF antagonists as drugs for treating septic disorders]

ABSTRACT OF THE DISCLOSURE [Abstract]

TNF antagonists are used to produce drugs for treating septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes.

COPY OF ALL CLAIMS

1. A method for treating those septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes, which comprises administering a therapeutically effective amount of a TNF antagonist.

2. The method as claimed in claim 1, wherein the serum level of interleukin-6 is 500 pg/ml and above in the measurement period.

3. The method as claimed in claim 1, wherein the measurement period is 4-10 hours.

4. The method as claimed in claim 1, wherein an $F(ab')_2$ fragment of a monoclonal anti-TNF antibody is used as TNF antagonist.

5. A kit comprising a TNF antagonist together with instructions for the use of this TNF antagonist for treating septic disorders where the serum level of IL-6 increases in a measurement period of at least thirty minutes.

6. A kit as claimed in claim 5, wherein a monoclonal anti-TNF antibody is used as TNF antagonist.

7. A method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonists, which comprises the following steps:

   (a) determination of the serum level of interleukin-6 in the patient at a first time t_1

   (b) determination of the serum level of interleukin-6 at a second time t_2 which is at least 30 minutes after the first time t_1, and determination of the ratio

$$V = \frac{\text{IL-6 level } (t_2)}{\text{IL-6 level } (t_1)}$$

   (c) treatment with TNF antagonists in the case where $V>1$.